CHEMICAL & ENGINEERING NEWS

C&EN

SEPTEMBER 19, 1994

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CHEMISTS STEP UP SEARCH FOR HALON SUBSTITUTES PAGE 29

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CHIRAL DRUGS

Single-isomer products drive development of new syntheses and separation techniques

Page 38

CHEMICAL & ENGINEERING NEWS

C&EN

SEPTEMBER 19, 1994

NEWS OF THE WEEK

■ EPA's draft report on dioxins reaffirms that the compounds are a probable cause of cancer in humans and finds other health risks. **Page 6**

■ Germany's Bayer buys key drug assets from SmithKline Beecham for $1 billion, regaining the right to use the Bayer name and logo in the U.S. **Page 7**

■ Researchers in France have developed an all-organic transistor that may lead to low cost, large-area, flexible plastic electronic devices. **Page 7**

■ Amgen and Corning are selected as corporate recipients of the 1994 National Medal of Technology. **Page 8**

■ Union Carbide ends financial ties to India with sale of shares in Union Carbide India Ltd., owner of the closed Bhopal plant where a methyl isocyanate leak killed and injured thousands. **Page 9**

■ Richard Mahoney, Monsanto's chairman and chief executive officer, will step down in March after 32 years with the company; Robert Shapiro has been named to succeed him. **Page 9**

COVER: Enantiomers of alanine modeled with Tripos' Sybyl software. Photo courtesy of Tripos

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BUSINESS

U.S. polypropylene producers face a challenging combination of increasing markets, production, and prices, and tight supplies of expensive feedstocks and shrinking exports. **Page 17**

Third-party evaluations of Responsible Care member companies to bolster trust in the program are being considered by the Chemical Manufacturers Association. **Page 19**

GOVERNMENT

National Research Council panel proposes that federal and state agencies use a single approach in deciding priorities for toxic waste site cleanups. **Page 23**

Legislation will be introduced to regulate companies offering invention promotion and marketing services. **Page 25**

SCIENCE/TECHNOLOGY

Defense Department presses for suitable alternatives as deadline approaches for banning manufacture of halons now used in military applications. **Page 29**

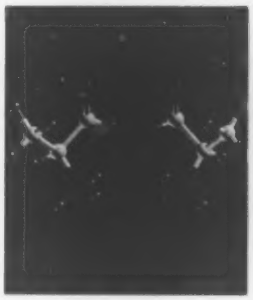
FDA says genetically engineered tomatoes are not significantly altered compared with other tomatoes; studies show insecticidal protein expressed in tomatoes is nontoxic to mammals. **Page 32**

New antioxidant additive for melt processing of resins, introduced by Ciba, boasts of better properties. **Page 35**

ACS NEWS

Twenty-six local sections received Phoenix Awards in recognition of their efforts in carrying out projects for National Chemistry Week. ƒ Investigations of five multiple terminations detailed in a report by the Subcommittee on Professional Standards & Ethics. ƒ Undergraduate activities at national meeting include a graduate school fair. ƒ October local section meetings featuring ACS tour speakers. ƒ Corrections for 8th edition of "Reagent Chemicals: ACS Specifications." **Page 73**

CHIRAL DRUGS



A steady, rising flow of single-isomer forms of chiral drugs is increasing the worldwide demand for enantiomeric intermediates and bulk active compounds, as well as enantioselective technologies and services. **Page 38**

LETTERS 4

CONCENTRATES

Business 11

Government 20

Science/Technology 27

THE DEPARTMENTS

Federal Alert 26

Software/Database Update 36

New Products 55

Meetings 81

Newscripts 104

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LETTERS

Don't blame immigration

A roundabout attempt was made in a letter by Kenneth Cohrs to attribute the unemployment trend of chemists to the Immigration Act of 1990, which increased the number of scientists and engineers admitted to the U.S. to 22,879 in 1992 from 14,100 in 1991 (C&EN, Aug. 22, page 5). However, there is a more direct answer to the question and possible solution to the problem.

The same issue reported that American Cyanamid and American Home Products have agreed to merge (page 7). Analysts have predicted that 10,000 jobs (about 13% of the combined work force) will be lost in this merger. In reality, the percentage of job loss during a merger was much higher in other reported cases. How many mergers have been completed in the chemical or manufacturing industries since 1991?

IBM alone has laid off more workers since 1990 than the total scientists and engineers allowed to immigrate to the U.S. It takes industrialists to create high-paying manufacturing jobs. DuPont, an immigrant, was one of them.

Chi-san Wu
Wayne, N.J.

ACS health plan

I am writing to encourage discussions among members and communication of their thoughts to their councilors regarding the formation of an ACS health care plan. Although ACS has tried several insurance plans in recent years, none of the non-life-insurance plans has the scope or impact that a health care plan would have for members.

The merits of such a plan are particularly strong for those of us working with companies undergoing consolidation (and the resultant layoffs), changing employers, working for employers who are unable to provide comprehensive benefits packages, recently unemployed, or self-employed.

The merits include stable health care plans for our families independent of our employers, continuity of coverage in the face of the fateful "preexisting condition" problem, participation in a very large group for economical rates, and not least, a very significant benefit associated with membership.

The problems of setting up such a plan are significant, including gaining corporate acceptance as another choice for employees where the company would contribute the same as it would to other offered plans. Given the large potential size of the group and the general good health of highly educated citizens, this plan may even be the plan of choice for small start-up companies, where many members are now employed.

I encourage you to initiate discussions exploring the feasibility of a members-only health plan. Now is the time to begin the informal discussions that lead to action.

Lee H. Latimer
Membership chairman,
ACS Philadelphia Section
Wayne, Pa.

Nonsense of proposals

As Pamela Zurer reports (C&EN, July 25, page 20), at least somebody at the National Institutes of Health has finally found enough common sense to raise the issue that we all know is long overdue. The battle, however, will not be easy because the very idea, "fund researchers, not proposals," is anathema for all the paper-shuffling bureaucracy and hence it is bound to face enormous logistical and political opposition.

Nevertheless, voices of dissent are growing. Nobel Prize physicist Leon Led-

Corrections

- July 25, page 24: Sepracor has an exclusive license on Jacobsen enantioselective catalysts for bulk quantities, but both Sepracor and Aldrich Chemical Co. are licensed to make, sell, and use research quantities of the catalysts.
- Aug. 15, page 16: The nylon fiber precursor plant in China's Liaoyang Province will have a capacity of 220 million lb per year, not 220,000 lb.
- Sept. 12, page 4: The National Medals of Science, which will be presented by President Clinton in October, are for 1994, not 1995.

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U.S. Polypropylene Producers Confront Troubling Supply-And-Demand Scenario

■ ***Rapidly growing demand, tight capacity, and raw material shortages test producers' ability to increase profit margins***

Ann M. Thayer,
C&EN Northeast News Bureau

Fina's polypropylene facility in La Porte, Tex., will be joined by a new plant in 1995.

To U.S. polypropylene producers, the waning days of summer are anything but. New capacity announcements, significant merger agreements, and booming end-use markets in the summer are being followed by early autumn price increases and even stronger demand growth.

But in an increasingly challenging market, events appear to be coming to a critical juncture. Tight raw material supplies, high costs for those feedstocks, and shrinking export markets make polypropylene a tough business in which to be profitable, despite production running at near maximum rates and rising prices.

Demand growth for polypropylene resins is expected to reach about 10% in 1994 and remain strong for the next few years, according to Houston-based consulting firm DeWitt & Co. "What we're seeing is positive economic growth virtually everywhere in the world and a market psychology that says plastics are going to be in shorter supply than they've been in the past," says Mark W. House, DeWitt's vice president for polymers. "Prices are going up ... and all of a sudden it becomes advantageous to buy all you can."

A relatively inexpensive and versatile material, polypropylene is used in a wide variety of products—automobiles, carpeting, diapers, medical equipment, rigid containers, and appliances. During 1994, about 9 billion lb of polypropylene are projected to be used in fiber, nonwoven, injection molding, and film applications. The Society of the Plastics Industry reported first-half 1994 polypropylene production at 4.64 billion lb, up 7.7% over first-half 1993, with sales and captive use up 10% to 4.91 billion lb.

However, polypropylene's growth—which is faster than that for most other resins, according to DeWitt—has not been driven by any particular end-use market area. Instead, overall U.S. market growth closely follows trends in gross domestic product growth and recent strong growth in all end-use areas. But as demand for polypropylene continues to increase, producers have been struggling to keep up. New production capacity is not expected to be in operation until late 1995.

The North American market for polypropylene is dominated by Himont, Amoco, Exxon, and Fina with a combined 55% of the 10 billion lb of nameplate capacity. Huntsman Chemical's pending acquisition of Eastman Chemical's polypropylene business, expected to close by Sept. 30, would place the company fifth among U.S. producers with an estimated capacity of more than 850 million lb.

Other producers are expected to strengthen their positions through capacity increases. Fina, an affiliate of the Belgium company Petrofina, announced in June that it would build a new 400 million-lb-per-year polypropylene facility at its plant in La Porte, Tex. Total polypropylene capacity at the site will be about 1.4 billion lb, making it the largest single polypropylene facility in the world when it is completed in late 1995.

Fina's La Porte plant will be the first of the new construction to go on-line. Formosa, delayed by licensing-related litigation with Phillips Petroleum, which holds a patent covering all U.S. polypropylene production, is expected to bring a 290 million-lb-per-year plant on-line this year at Point Comfort, Tex.

"At [current demand growth] rates, the industry needs two world-scale plants built a year," says H. Patrick Jack, Fina vice president for chemicals, who is concerned about the U.S. industry's ability to meet demand. The industry is already operating at a 93 to 95% capacity utilization rate, near maximum for polypropylene production because of technical limitations. "The industry is, in effect, running at all available capacity. There is just no more left," he adds. Even at the peak period for expansion, estimated by DeWitt to be 1996 and 1997, demand growth will still outpace capacity growth by about 2% per year.

Other construction announced is by Phillips Sumika Polypropylene, a 50-50

partnership between Phillips Petroleum and Sumika Polymers America, a unit of Sumitomo Chemical. In August, the partnership said it will add a new 270 million-lb-per-year plant at Phillips' Houston chemical complex to be completed in 1996. Also by 1996, Epsilon Products will double capacity, to 720 million lb, at its Marcus Hook, Pa., plant.

Another approximately 300 million lb of capacity is expected to be added between now and the end of 1995 through process improvements, says House. Aristech will increase capacity by 120 million lb per year at its Neal, W.Va., site. Seadrift Polypropylene, the Shell-Union Carbide joint venture, is expected to make gains of 35 million lb in early 1995 and another 65 million lb at the end of 1995 at its Texas plant. This year, Huntsman is increasing capacity by 40 million lb at its Woodbury, N.J., facility.

More expansions are anticipated in the next few years, especially since producers finally are achieving price increases under the tight supply-and-demand situation. Prices increased 3 cents per lb in March, another 3 cents in June, and again in September. Another increase is expected Oct. 1, which will bring prices up to more than 35 cents per lb.

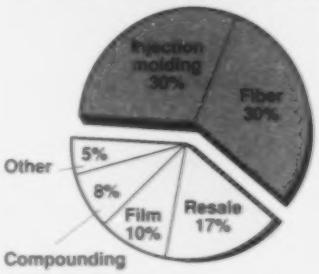
"There probably will not be any relief or plateau effect in polypropylene pricing rises until new production comes on-line in early 1996," says House. "That's the first drop in operating rates that I can foresee, so I expect supply and demand to be tight and pricing direction to be strong until that time." The strong pricing outlook is a significant change from the lack of price increases and profitability that has plagued polypropylene producers for the past few years.

In the late 1980s, following a period of price increases, capacity expansions in Latin America and Asia-Pacific resulted in a global market shift and an oversupply situation for U.S. markets. U.S. producers went from exporting about 21% of production in 1988 to about 6.6% today, according to DeWitt. The result was a tremendous drop in prices, back to mid-1970s levels, and extremely tight profit margins for several years.

John Hubby, general manager of Phillips Sumika, fears that a similar scenario could happen again. "A lot of [U.S. market growth] is being driven by low prices, quite honestly," he says. "So at some point, U.S. demand could get stalled out if prices go too high too quickly." Competition then could come from other plastics, which are also seeing price increases, or alternative materials such as glass, paper, and metal.

"The only consolation we've got is that the cycles appear to be lengthening out, [they are] not quite as abrupt as they may have been in the past. However, a concern is that the peaks may be there, but they may not last as long and the troughs last longer," adds Hubby.

Most polypropylene is used in molding and fiber



Total U.S. consumption of polypropylene[a] = 8.49 billion lb

a May 1993 through April 1994
Source: DeWitt & Co.

U.S. polypropylene market led by few producers

Millions of lb	Capacity 1994	Capacity 1996[a]	% change 1994–96
Himont	1,018	2,006	5%
Amoco	1,660	1,660	0
Exxon	1,027	1,027	0
Fina	959	1,356	41
Aristech	721	985	37
Phillips Sumika	480	750	56
Eastman Chemical	441	441	0
Solvay	441	441	0
Huntsman	386	399	3
Epsilon	360	720	100
Shell	340	340	0
Quantum	300	300	0
Lyondell	300	300	0
Seadrift	198	298	50
Formosa	154	496	222
Rexene	150	150	0
Novacor	141	141	0
IGI Baychem	66	66	0
TOTAL	10,042	11,876	18%

a Includes as yet unannounced expansions.
Source: DeWitt & Co.

"The [trough] that we are just coming out of is the longest yet, and two or three years without making any money [makes] people begin to wonder whether it's the right business to be in at all."

Business planning and decision-making are more difficult under current market conditions, says Brad Jones, Huntsman's sales and marketing vice president for polypropylene. And other managers suggest that customers should be careful about their long-range planning and be sure of secure supply sources before going ahead with their own expansions. "We're very concerned about the ability of our customers to pass along the price increases," he says.

"Our customers are in a tenuous position right now. We are supplying them with data and market information ... so that they're able to communicate effectively to their customers why prices of polypropylene products are going up," says Jones. However, he does not have the same concern as Hubby about demand dropping due to high prices. "Polypropylene today is still less expensive than it was five years ago. In a relative sense, polypropylene continues to be one of the lower cost commodity products versus other polymers and alternative materials."

Profitability depends more on margins—the difference between selling prices and the combined costs of operating and raw materials—than on the ability to raise prices. Currently, rising propylene prices are contributing to increases in resin prices, but also continuing to seriously pinch margins. Three U.S. steam cracker outages—by Exxon, Shell, and Amoco—are severely affecting ethylene supplies and also are having an impact on propylene supply and pricing.

Hubby characterizes the raw material supply situation as "a little bit of a panic," whereas Fina's Jack calls it a crisis. "The raw material costs have already started going up, and that will continue through the end of the year and likely into the first quarter of next year," predicts Jack. "Polypropylene has just barely kept up with increases in raw material costs so far this year."

However, producers are optimistic that polypropylene margins will eventually improve above the few cents per pound they are seeing now. And they hope to see the capital needed for investing in new capacity. The picture has to get better, agrees Jones, "because if it doesn't, the shortage will be longer and harder." □

Chiral Drugs

Stephen C. Stinson,
C&EN Northeast News Bureau

New single-isomer products on the chiral drug market create demand for enantiomeric intermediates and enantioselective technologies

A number of trends characterize today's chiral drug industry. Perhaps the most important one is that a steady, rising flow of single-isomer forms of chiral drugs onto U.S. and world markets is creating an increasing demand for enantiomeric intermediates and bulk active compounds as well as enantioselective technology and services.

Another trend reflects the situation throughout the chemical industry—that of partnering. Specifically, in the chirotechnology industry of small and not so small firms that have grown up to serve drug companies, formal and informal alliances are being forged among firms that have different and complementary capabilities. And in asymmetric technologies, interest is unexpectedly surging in chromatographic separations as economically viable methods to make multiton quantities.

Meanwhile, in the coming age of managed health care, the big winners will be companies that make chiral drugs and seven-day adhesive plastic film skin patches formulated with single isomers of chiral drugs, according to Richard L. DiCicco, president of the consulting firm Technology Catalysts, Falls Church, Va. A number of factors back up DiCicco's prediction: Single enantiomers can be more selectively effective; skin patches contain much less drug and therefore can be less expensive to produce; and skin patches make patient compliance with drug regimens easier.

And DiCicco says that inventors of new, higher priced, patent-protected enantiomeric drugs can use them as bargaining chips with managed health care networks to maintain sales and prices of older, off-patent drugs. As an example of how this tactic works, DiCicco cites the marketing link by Ciba-Geigy in Switzerland of its off-patent anti-inflammatory drug diclofenac with its patent-protected transdermal nitroglycerin skin patches to treat angina (stress-induced chest pains of heart disease). DiCicco says Swiss purchasers get deep discounts on normally high-priced, patented skin patches if they also buy diclofenac at list price. DiCicco realizes that nitroglycerin itself is achiral. But he gives it as an example of marketing opportunities for chiral drugs.

DiCicco estimates the 1993 worldwide market for chiral drugs at $35.6 billion, a growth of 22% over 1992 alone. These figures are for shipments of dosage forms from producers' factories. DiCicco expects the market to grow at 5% per year to about $40 billion in 1997. But this is his conservative rate of growth. The estimate includes only growth of those compounds already approved by drug authorities worldwide, and not entries of agents that may be approved between now and 1997. Including these "to-be-approved" drugs, the 1997 chiral drug market could hit $60 billion, according to DiCicco.

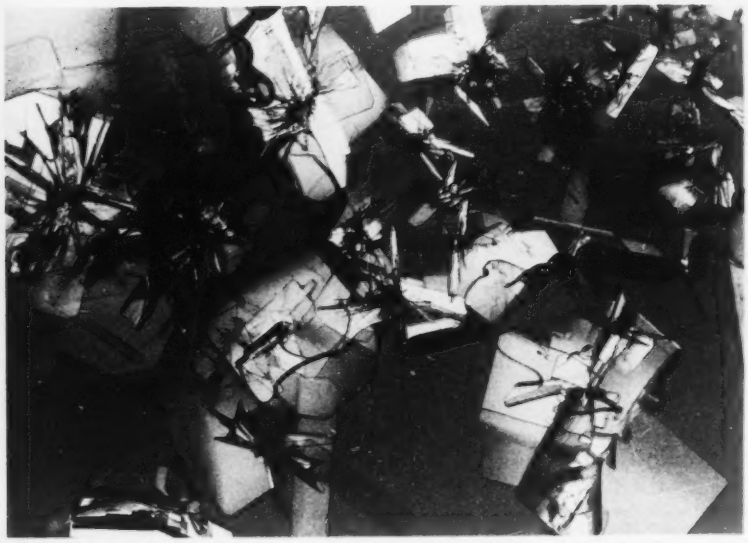
Such hedging as DiCicco's about whether to posit higher or lower estimates of the value of the chiral drug market comes from a new mood of uncertainty that has fallen over the drug industry. There has always been uncertainty as to the exact time when regulatory agencies would approve drugs that are new chemical entities. But now there is also uncertainty about whether and when agencies will approve single-isomer forms of drugs like ibuprofen that are already approved as racemates—the so-called racemic switches.

A lot of the projected growth of the chiral drug market rides on the success of racemic switches. For example, DuPont Merck Pharmaceutical Co., in Wilmington, Del., projects that the lysine salt of analgesic (*S*)-(+)-ibuprofen has the potential to be a $1 billion-per-year over-the-counter (OTC) drug. But the company has experienced long and unexpected delays while its new drug application (NDA) for the compound languishes at the Food & Drug Administration. And Sepracor, Marlborough, Mass., has assembled a stable of almost two dozen racemic drugs produced by other companies. Sepracor has redeveloped and patented the drugs in single-isomer forms and now seeks to license them.

Sales of enantiopure drugs top $35 billion

$ Billion	1993 world sales[a]
Cardiovascular	11.3
Antibiotics	10.8
Hormones	4.5
Central nervous system	2.0
Anti-inflammatory	1.5
Anticancer	1.0
Other[b]	4.5
TOTAL	35.6

a Wholesale finished dosage forms. b Includes vitamins, amino acids, immunosuppressants, peptide drugs, anti-glaucoma drugs, and plant extracts.
Source: Technology Catalysts



Bifonazole crystals imaged with a polarizing microscope. Bifonazole is a chiral antifungal drug developed and marketed by Bayer.

In addition, some industry observers tell C&EN that there is mutual uncertainty among drug companies and FDA about policies to strive for in chiral drug approvals. For example, these industry observers say that approval for (*S*)-(+)-ibuprofen is slow in coming because FDA reviewers have not decided on a policy for dealing with racemic switches.

On the matter of how much of the "other" enantiomer FDA will allow in a drug, FDA spokesmen say the agency will balance synthetic convenience with the toxicity of the other enantiomer. Within the companies, some argue for approval of lower but adequate enantiomeric purities to make production within set specifications economically feasible. But others would like to push for ever higher enantiomeric purities in an effort to keep the qualities of their existing chiral drugs forever beyond the reach of generic competitors.

Although it is an example of purity of substance and not enantiomeric purity, DiCicco cites the immunosuppressant drug cyclosporin A marketed by Sandoz Pharmaceuticals Corp., East Hanover, N.J., as a case of how this latter tactic can work. The drug was originally approved with a specification of 97.5% purity. But in 1992, Sandoz filed what is called an in-process revision, setting a new purity specification of 98.5%. Generic drugmakers who want to market cyclosporin A must now find a source of 98.5% cyclosporin A and do their clinical equivalence testing on that.

The overall climate of uncertainty has led some to question whether the long-predicted boom in chiral drugs will actually happen. The question is whether the market will grow at only a moderate pace, limited by the number of new chemical entities in the pipeline, or whether the market will have the added fuel of numerous racemic switches.

Ton Wijsman, president of DSM Fine Chemicals, Saddle Brook, N.J., told an audience at Chiral USA '94 in Reston, Va., in May that the answer probably is slow market growth based on new chemical entities with little help from racemic switches. DSM is a large supplier of chiral drug intermediates, accounting for almost half of the $1.5 billion to $2 billion U.S. market, including intermediates for the cardiovascular drugs captopril and diltiazem; antibiotics amoxicillin, ampicillin, cefaclor, cefadroxil, and cefalexin; and the antiglaucoma drug timolol.

To make his point, Wijsman has added up the 95 best selling U.S. drugs based on drugstore sales. He notes that 36 single-isomer drugs on the list are new chemical entities that were approved between 1990 and 1993. Seven were approved in 1990, nine in 1991, 13 in 1992, and seven in 1993—an average of nine per year—indicating to Wijsman that there was no growth in numbers of single-isomer compounds during the four-year period.

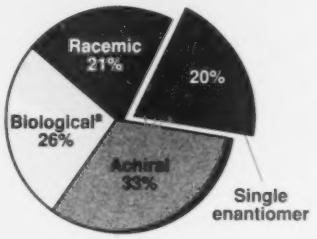
Wijsman also notes that the many expected racemic switches among β-adrenergic blocking agents to treat high blood pressure and heart disease have not materialized. And in addition to (*S*)-(+)-ibuprofen, several racemically switched "profens" (β-phenyl- and other β-arylpropionic acids) await U.S. approval, he says. Among the many already approved racemic drugs redeveloped as enantiomers by Sepracor, none has been approved and launched. Notably, Eli Lilly & Co., Indianapolis, shows no interest in licensing the (*S*)-fluoxetine isomer of its antidepressant drug Prozac.

By contrast, DiCicco argues that large-volume growth in chiral drugs is coming and hinges only on timing. He notes that G. Broschek Gebro of Tirol, Austria, has already launched (*S*)-(+)-ibuprofen in that country. And FDA has just approved marketing of the Aleve brand of the sodium salt of (*S*)-(+)-naproxen as an OTC analgesic drug by the joint-venture company Procter-Syntex Health Products, Cincinnati. This is not strictly a racemic switch, because the Anaprox brand of this enantiomeric compound had previously been approved and marketed as a prescription drug by Syntex Laboratories, Palo Alto, Calif. But DiCicco says this approval lights the way toward U.S. approval of (*S*)-(+)-ibuprofen and a host of other profens after that. As for delays or cancellations of racemic switches for β-adrenergic blockers, DiCicco says these compounds were rendered unnecessary by introductions of other enantiomeric drugs for heart disease—angiotensin-converting enzyme (ACE) inhibitors—into skin patches.

All of this activity in developing new chiral drugs has resulted in soaring demand for certain highly specialized intermediates. DiCicco cites enantiomers of glycidol (2,3-epoxypropanol), glycidyl triphenylmethyl ether, 2,3-isopropylideneglycerol (2,2-dimethyl-3-hydroxymethyldioxolane), and 3-aminoquinuclidine (3-amino-1-azabicyclo[2.2.2]octane) in particular.

Glycidol is an intermediate on the way to several interesting compound classes. DiCicco estimates world demand at 10,000 kg yearly, of which 5,000 kg alone is for research. The major source for the alcohol has been Daiso Co. of Osaka, which has dropped out of

Single enantiomers are 20% of best selling drugs



Total number of drugs = 95

Note: Figures are for 95 best selling drugs according to U.S. drugstore sales, excluding hospitals and international sales. **a** Sources are biotechnology, fermentation, and extraction. **Source:** DSM Fine Chemicals

supplying it in favor of producing more profitable glycidyl derivatives.

The upsurge in demand for the triphenylmethyl (trityl) ether may result from the ease with which this group comes off after reaction of the epoxy group. And 2,3-isopropylideneglycerol is seen as a replacement for glycidol. Substituted benzamides of 3-aminoquinuclidine are in tests as next-generation antipsychotic drugs. They act by binding to brain nerve cell receptors of the neurotransmitter 5-hydroxytryptamine (serotonin) of a type called 5-HT_3.

Chiral separation techniques

Activity to develop chiral drugs has also led to progress in manufacturing them and their enantiomeric precursors. A recent surprise is the emergence of liquid chromatographic methods from relative disfavor to become highly promising ton-scale processes.

One reason for the former disfavor is that any separation of enantiomers from a racemate results in the waste of the unwanted enantiomer, a waste of 50% of the material. Only the possibility of finding a use for the "other" isomer or of racemizing the unwanted enantiomer and recycling it through the separation process can improve the cost-effectiveness of this situation. Furthermore, cost is a reason for disfavor since liquid chromatography uses large quantities of solvents.

But sometimes the asymmetric synthetic route to a drug or intermediate is so difficult that separation of a racemate turns out to be the cost-effective solution. Verapamil is one such case. The racemate has long been approved as a calcium channel blocker to treat high blood pressure, angina, and abnormal heart rhythms. The (*S*)-isomer alleviates high blood pressure even more effectively than the racemate, while the (*R*)-form is now found to inhibit resistance of cancer cells to anticancer drugs.

As in other parts of the chirotechnology industry, enantioselective liquid chromatography is a mosaic of alliances between firms with complementary technologies and ties to inventive academic chemists. In the matter of enantioselective column packings, for example, Tokyo-based Daicel Chemical Industries has teamed with chemistry professor Yoshio Okamoto of Nagoya University. Daicel's U.S. subsidiary is Chiral Technologies, Exton, Pa.

Daicel-Okamoto packings depend on cellulose backbones to impart the chiral environment. To make Chiralcel OD, for example, Daicel reacts cellulose with phosgene to attach up to three pendant chloroformate ester groups to each glucose unit. Reaction next with 3,5-xylidine forms 3,5-dimethylphenylcarbamate groups, which give the packing the appropriate affinity to separate enantiomers of aromatic, carbonyl, cyano, hydroxy, nitro, and/or sulfonyl compounds.

Regis Technologies, Morton Grove, Ill., has commercialized enantioselective packings invented by organic chemistry professor William H. Pirkle of the University of Illinois, Urbana-Champaign. Pirkle columns feature enantiomeric compounds called chiral selectors that are covalently bound to silica gel. Pirkle designs each chiral selector to provide three different types of noncovalent binding to racemate molecules.

For example, the packings that Regis offers under the names (*R,R*) or (*S,S*) Whelk O1 contain a naphthalene nucleus and a 3,5-dinitrobenzamide group. The naphthalene interacts with racemate molecules by π-electron donation, the dinitrophenyl by π-electron acceptance, and the amide group by hydrogen bonding. Pirkle justifies three as the number of binding interactions needed because the chiral selector must recognize the front and back, top and bottom, and both sides of each molecule coming past.

Advanced Separation Technologies, Whippany, N.J., continues to bring out packings developed by analytical chemistry professor Daniel W. Armstrong of the University of Missouri, Rolla. Armstrong's most recent products, which Advanced Separation will introduce this fall, are based on the macrocyclic antibiotics rifamycin B and vancomycin as chiral selectors linked to silica gel. Armstrong depends on the complexity of these molecules to offer several different binding interactions at once: π-π complexation, hydrogen bonding, inclusion in a hydrophobic pocket, dipole interactions, and/or steric repulsion.

The obvious application of all these packings is conventional column liquid chromatography for analysis or production. But Daicel/Chiral Technologies and Sepracor, which also specializes in chiral separations, are seeking partners to use such packings in what is called simulated moving bed chromatography.

Directory locates sources of chiral compounds

For anyone looking for sources of enantiomeric compounds for production of chiral drugs, "The R-S Directory," 2nd edition, is an 89-page, spiral-bound compilation of more than 1,000 enantiomeric intermediates, auxiliary reagents, and resolving agents produced by more than 50 companies. The directory is indexed by compound name, molecular formula, and producer name. It supplies addresses as well as telephone, fax, and telex numbers of producers, including those of branch offices and subsidiaries of foreign firms in the U.S. and/or Europe.

The directory does not list such common, naturally occurring compounds as terpenes, L-amino acids, or even protected amino acids. However, other chemical derivatives of such natural products are included. Also not listed are laboratory chemical supply houses. Thus Sigma Aldrich, a laboratory chemical supply house that is also a basic producer of chiral compounds, is a notable omission. The booklet can be purchased for $115 by ordering from The R-S Directory, P.O. Box 153, Purley, Surrey CR8 5YN, England.

Though an awkward description, "simulated moving bed" has 30 years of engineering tradition behind it in petrochemical and food processing, so it is certain to find wide use in the chirotechnology industry. The idea is that in normal chromatography the liquid carries the sample forward through a stationary bed of packing. If the column length is sufficient, the components in the sample become separated according to their relative affinities for the packing material.

Simulated moving bed refers to a technique that behaves as if the packing were moving backward at the same time. If that were possible, the column could be shorter. In the actual process, the bed of packing does not move. Rather, the front and back ends of the column are joined to form a circle. And the operator moves the points of injection of fresh sample, injection of fresh solvent, and removal of components of the mixture around the circle.

To use an analogy, the process is like the sequential turning on and off of light bulbs on a theater marquee. The pattern of lights appears to move around the marquee, although the light bulbs themselves do not move.

To resolve a racemate, the operator injects a bolus of the racemate into the circular column, where the solvent is already being pumped along. After a time, the bolus moves part way around the circle and separates incompletely into two peaks. The moving front contains one pure enantiomer, and the tail contains the other. Calculating where the bolus is in the circle, the operator withdraws portions from the front and tail as products, injects new racemate into the center of the bolus, and replenishes the solvent with an injection at a part of the circle away from the moving bolus. After a time sufficient for new partial separation, the operator repeats the sequence of injections and withdrawals at the appropriate parts of the circle.

Mark J. Gattuso, business development manager at UOP, Des Plaines, Ill., says UOP received its first patents on its Sorbex simulated moving bed technology in the 1960s. UOP is cooperating with Chiral Technologies to apply the process to resolution of racemates, though no formal agreement has been reached between the two companies.

Speaking at the Chiral Europe '94 conference this month in Nice, France, Gattuso said that among the company's two dozen versions of the process applied to petrochemical, food, and drug separations, UOP has licensed 53 plants to separate *p*-xylene from C_8 aromatics, 33 to separate *n*-paraffins from branched and cyclic hydrocarbons, six to separate olefins from paraffins, five to separate fructose from corn syrup, and one to purify citric acid. His point is that, after 30 years of such successes, a simulated moving bed approach will also work in enantioselective separations. As to economics, Gattuso says process costs are less than 10 cents per kg at a 100,000-metric-ton-per-year plant and 15 cents at 15,000 metric tons per year.

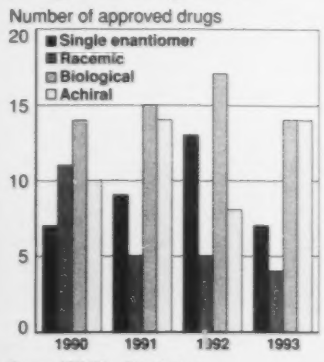
Besides the informal cooperation between Chiral Technologies and UOP, Sepracor has a similar loose alliance with Separex Chimie Fine of Champigneulles, France. Separex offers two units, the Licosep 1½, which is capable of separating 10 to 400 g of racemate per 24-hour day, and the Licosep ½₀, with a capacity of 500 g to 25 kg per 24-hour day. The two systems have 12 "small" or eight "large" chromatographic columns, respectively, in a loop. At each junction of the columns are four valves to accommodate injections of racemate and solvent and withdrawal of products. A microcomputer uses Separex software to operate the valves in sequence.

The French company recently resolved the drug intermediate 2,3-epoxy-5-methoxytetralin under a contract with Sandoz of Basel, Switzerland, using methanol solvent and cellulose triacetate column packing. The yield of desired enantiomer was 100%, based on its total content in the racemate, compared with 70% by conventional chromatography. Consumption of methanol was 320 g per gram of racemate compared with 2.4 kg for conventional chromatography. The economy of solvent consumption results from the 15 times greater concentration of racemate that is possible in this cyclic process than in conventional liquid chromatography.

Separex president Roger-Marc Nicoud estimates that costs of simulated moving bed resolutions of racemates might be $100 to $1,000 per kg on a scale of 500 kg per year. This cost range is much higher than for xylenes or fructose because economies of scale are lacking and labor costs are a larger proportion of the total on the small scales involved.

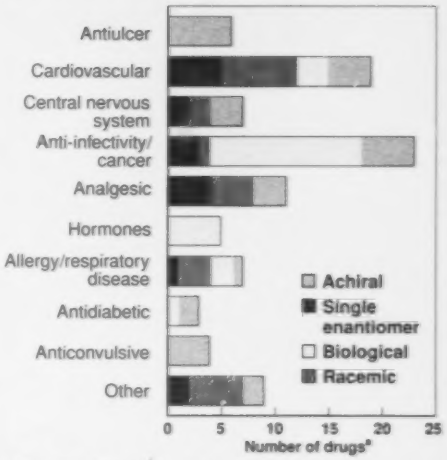
Aside from developments in simulated moving beds, Akzo Nobel International Research, in Arnhem, the Netherlands, has developed an enantioselective countercurrent extraction technique capable of scaling up to ton quantities. Marketing manager Mirjam S. Leloux described the process at the

Biological products lead drug market growth



Source: DSM Fine Chemicals

Proportion of chiral drugs sold varies with therapeutic class



*Best selling drugs according to drugstore sales.
Source: DSM Fine Chemicals

Chiral USA '94 conference in Reston.

In one experiment, two heptane solutions in a cell flow parallel to one another, in opposite directions, separated by a membrane. The membrane is water-saturated cellulose. One heptane solution is 10% in dihexyl D-tartrate and the other is 10% in dihexyl L-tartrate. Racemic norephedrine (2-amino-1-phenyl-1-propanol), a decongestant drug, is added to one of the solutions.

Heptane solvent and dihexyl tartrate solutes are hydrophobic and cannot cross the water-saturated membrane. The fairly polar amino-alcohol norephedrine crosses the membrane back and forth. As liquid flow continues, each enantiomer of norephedrine is concentrated on the side of the membrane containing the tartrate enantiomer with which it has the greater affinity.

In the laboratory, Akzo Nobel chemists use commercial dialysis cells in which the membrane is a narrow tube passing concentrically through a larger shell. One solution flows through the tube, the other outside through the shell. Akzo Nobel workers connect as many cells in series as are needed to obtain separation. In addition to dihexyl tartrates, other possible hydrophobic chiral selectors include O,O-dibenzoyltartaric acids, polylactic acids, dimethyl 2,3-isopropylidenetartrates, and fenchones.

Leloux points out that a small apparatus can separate several grams of drug for toxicity and preclinical testing, and later the process can be scaled up to produce commercial amounts. This use of the same method throughout will simplify the process of satisfying regulatory requirements, she says. Akzo Nobel seeks to license the technology to drug company users.

Chromatography analyses

In addition to its new promise as a production process, liquid chromatography has become the drug industry's method of choice to determine enantiomeric purity. Classical optical rotation has been dismissed because of unreliable dependencies on temperature, solvents, and concentrations. And nuclear magnetic resonance spectrometers are costly to tie up routinely.

In the matter of chiral drug analysis, chemistry professor Christian Roussel of the University of Aix in Marseilles, France, has assembled a database of liquid chromatographic chiral separations to aid chemists in fast pinpointing of detailed analytical methods that work. Roussel notes that there are basically two types of chiral column packings. One is the Pirkle or Armstrong type with an enantiomeric chiral selector bound to an achiral substrate such as silica. The second is a chiral polymer like a polysaccharide (as in the Daicel approach), protein, or synthetic resin made from an enantiomeric monomer or by chiral polymerization. Of the 560 packings cataloged in his Chirbase, about half are silica based and half are chiral macromolecular. Among the 560 packings, 110 are commercially available.

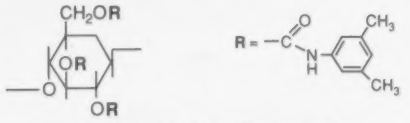
The database includes descriptions of 24,000 individual analytical separations, and Roussel and his coworkers add to these at the rate of 4,000 per year. And 8,000 structures of compound's enantiomers have been chromatographically separated and are archived. Database searches are molecular-structure oriented. Users can enter their own data into their copies of Chirbase.

The Chirbase client either uses an IBM 386-compatible computer on a local version called ISISBase or accesses the database via Ethernet on a VAX minicomputer in Marseilles, which offers even more versatile software and search techniques. One search type is for an exact structure match. Widening the search, the user may stipulate that isomers, tautomers, or parent compounds of the target molecule are allowed. A second search type is by substructure, in which the user sequentially builds an "R-group" based on structural features of the analyte target molecule and responses from the database. A third search is by similarity, in which the user is guided to estimate a percent similarity that is permitted. The program then furnishes chromatographic conditions that have succeeded on compounds in that range of similarity.

Whether chromatographic or other, drug companies will usually have to develop enantioselective analyses for both single isomers and racemates of chiral drugs. Jeffrey J. Blumenstein of

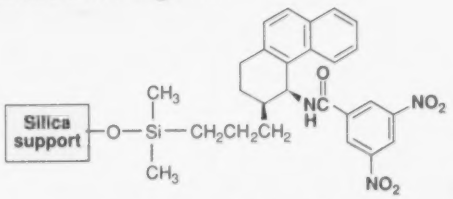
Enantioselective column packings vary in molecular design

Daicel packings are cellulose based



Chiralcel OD, Chiral Technologies

Pirkle packings derive selectivity from threefold bonding sites



(*S,S*) Whelk-O1 CSP, Regis Technologies

■ Electron donor group ■ Electron acceptor group
■ Hydrogen-bonding group

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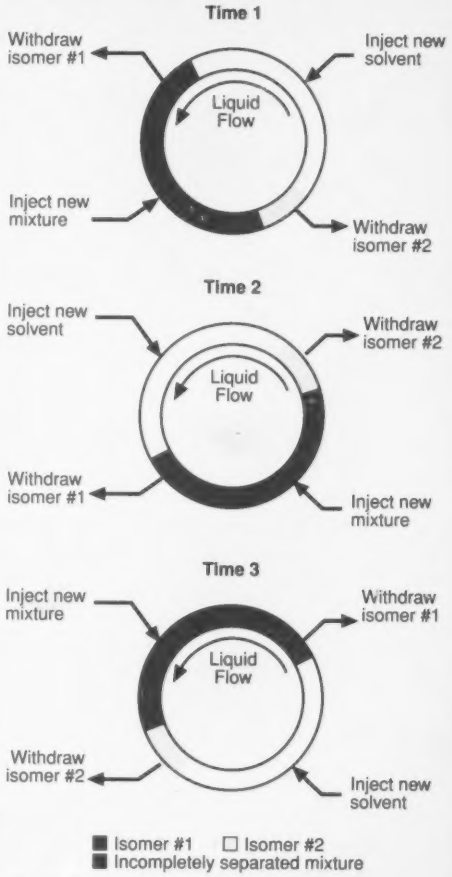
FDA's Office of Drug Evaluation says that such analyses may have to be done on both the bulk active substance, the dosage form of the drug, and any key intermediates. And such analyses should include tests of identity and assays of how much drug and how much of a single isomer is in a sample.

Among drugs generally, there are many criteria to decide whether a starting material or intermediate is "key." But as to chiral drugs, Blumenstein says any synthetic step that introduces an asymmetric center renders that product as key. And subsequent reactions and their products that have the potential to change the configuration at the asymmetric center will also bring the requirement for enantioselective testing of those products.

But Blumenstein also says that intermediates and some drugs with multiple stereogenic centers may not need stereoselective analyses. This is because it is unlikely that both asymmetric atoms of a molecule with two such atoms will undergo a change to the opposite configuration at once. Therefore, if only one atom changes, the result is a diastereoisomer and not an enantiomer of the changed compound. And presence of diastereoisomers can be detected by achiral methods.

Cycling sequence makes column seem to 'move backwards'



Source: UDP

1. After each injection of fresh mixture, the flow of liquid begins some separation of components.

2. At the appropriate moment, a sample of enriched component is drawn off as product.

3. Valves placed at strategic locations around the looped column allow the operator to time injections and withdrawals.

Nonlinear enantioselective effects

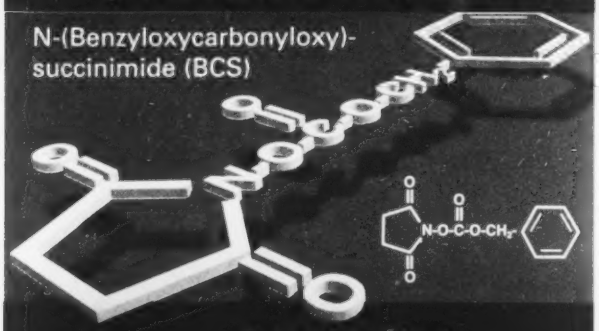
Just as the emergence of simulated moving bed techniques has changed the fortunes of liquid chromatography in drug production, so, too, a new awareness of nonlinear effects has changed the landscape of asymmetric synthesis in general. Among these nonlinear effects is one called asymmetric amplification. This means that use of a catalyst or reagent with low enantiomeric purity may yield a product of higher enantiomeric purity.

The question of asymmetric amplification has become a factor in the patent position of Aldrich Chemical, based in Milwaukee, with respect to enantiomeric organoboranes. In 1987, organic chemistry professor Herbert C. Brown of Purdue University developed and patented both enantiomers of diisopinocampheylchloroborane as asymmet-

opportunities

for peptide synthesis and pharmaceutical intermediates

N-(Benzyloxycarbonyloxy)-succinimide (BCS)



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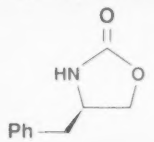
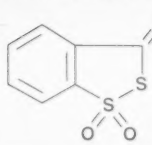
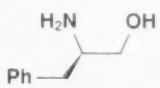


3H-1,2-Benzodithiol-3-one-1,1-Dioxide

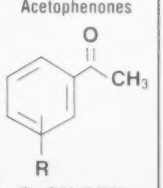


Beaucage Reagent

(R)-Phenylalaninol

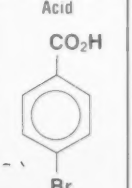


3-Substituted Acetophenones

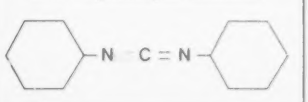


R=OH,OCH$_3$

4-Bromobenzoic Acid



N,N-Dicyclohexylcarbodiimide



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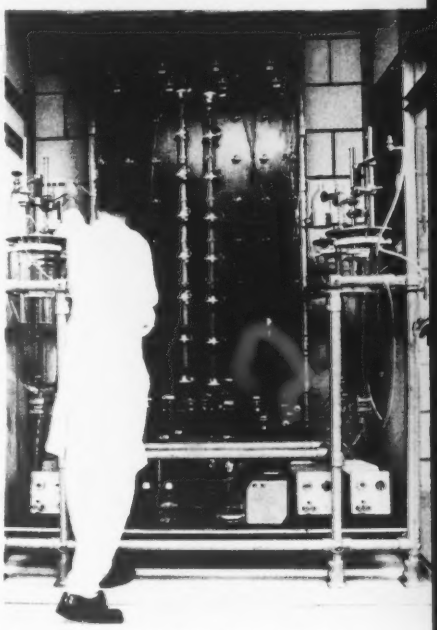

Researcher at Akzo Nobel International Research checks behavior of the company's proprietary countercurrent extraction columns for separation of enantiomers from racemates.

ric reducing agents of ketones to secondary alcohols. Despite the forbidding name, these reagents are conveniently available from diborane and either enantiomer of α-pinene.

Aldrich Chemical has a license on the Purdue patents and markets the reagents under the tradename DIP Chloride. In particular, one patent describes the production of DIP Chloride, and another covers its use in greater than 95% enantiomeric excess to produce secondary alcohols in similarly high enantiomeric excesses. Organochloroborane of this high enantiomeric excess is hard to make, because the air- and moisture-sensitive compound must be laboriously crystallized after synthesis from pinenes from natural sources of lesser enantiomeric purities.

Meanwhile, Callery Chemical, Evans City, Pa., has invented an alternative route to produce diisopinocampheylchloroborane. And developments at Merck & Co., Rahway N.J., may have shot away the protection of Aldrich's high-enantiomeric-excess patent. In 1991, medicinal chemists at Merck reported that reagent made with α-pinene of only 70% enantiomeric excess reduced a ketone to a secondary

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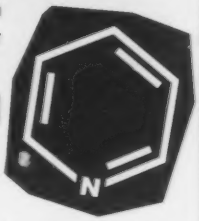

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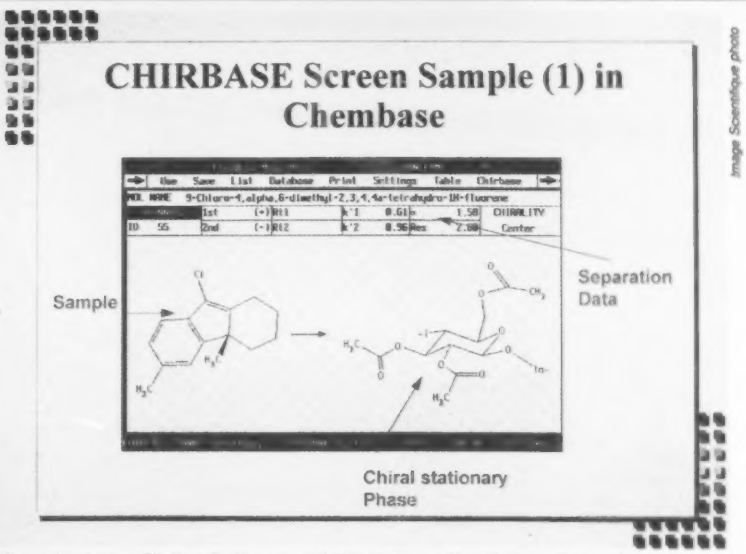


Image Scientifique photo

Computer screen display during a search for optimum liquid chromatographic separation conditions on Chirbase, developed at the University of Aix, Marseilles, France. The structure at left is the compound analyzed and the structure at right is the chiral column packing used. Also given are the literature reference and exact conditions.

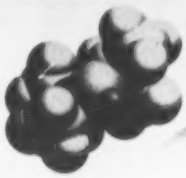
alcohol in greater than 98% enantiomeric excess. The implication is that unanticipated asymmetric amplification makes pinenes of high enantiomeric purity unnecessary. Nevertheless, Callery is going ahead with negotiating an agreement with Aldrich to gain access to organoborane technology at all levels of enantiomeric purity.

Organic chemistry professor Henri B. Kagan of the University of Paris-South, in Orsay, France, has contributed a great deal to the understanding of asymmetric amplification and other chiral nonlinear effects. He described his newest results at the chiral conference in Nice. His most surprising finding is that catalysts and reagents may exist that give worse enantiomeric purities when they themselves are enantiomerically pure than when those agents are less than enantiomerically pure.

As an example, most chiral catalysts and reagents have two or more molecules of enantiomeric ligand, L, bound to a metal, M. In the Aldrich and Callery boranes, boron is the "metal."

If the ligands are enantiomerically pure, then the catalyst or reagent is either all $M(L_R)_2$ or $M(L_S)_2$. But if a ligand that is nominally L_R is present in only 50% enantiomeric excess, then there are just three molecules of L_R in the mixture for every one of L_S. So the catalyst or reagent is on average a 50-50 mixture of $M(L_R)_2$ and ML_RL_S.

If $M(L_R)_2$ is an active agent, and if ML_RL_S is relatively inactive, then the enantiomeric purity of the reaction product will be decided by L_R to an ex-



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tent greater than its presence in the catalyst or reagent. The effect of L_R is amplified. A graph of enantiomeric purity of product versus catalyst or reagent will be curved, not linear.

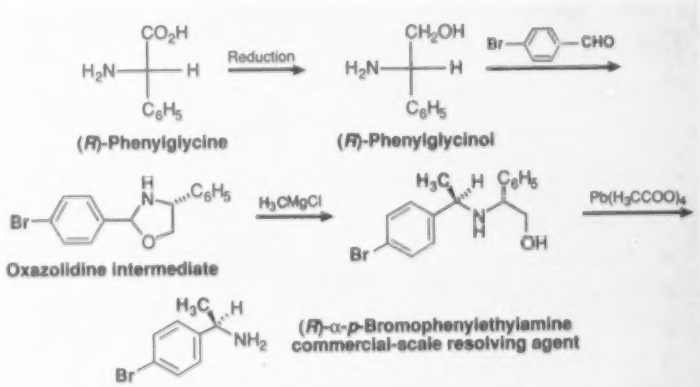
Kagan has also done the mathematics for an agent that is ML_4. In this case, there is a possibility that the graph of enantiomeric purity of product versus that of agent will be doubly curved. Thus an enantiomerically pure catalyst or reagent could theoretically give worse results than a less pure one. No such case has yet been observed, and the mathematics may be academic. But events of the past few years have changed nonlinear chiral effects from academic curiosities to important factors in drug research and patent law.

A recent on-purpose design of what might be called an asymmetric amplification is "chiral poisoning" of a cheap racemic hydrogenation catalyst in order to avoid use of a costly enantiomeric catalyst [*J. Am. Chem. Soc.*, **115**, 804 (1993)]. Organic chemistry professor John W. Faller of Yale University starts with racemic 2,3-bis(diphenylphosphino)butane, which is nicknamed chiraphos. He complexes chiraphos with rhodium to make the catalyst. Then he adds half an equivalent of a diphenylphosphino derivative of L-methionine.

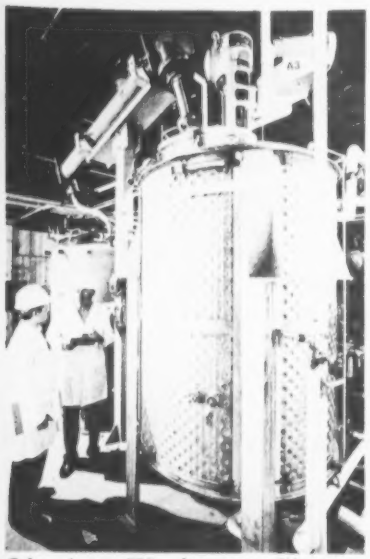
The chirality of enantiomeric methionine causes it to complex preferentially with one enantiomer of racemic chiraphos-rhodium catalyst. The sulfur of methionine poisons the catalytic activity of the chiraphos-rhodium enantiomer with which it reacts. The low cost of methionine makes the enantiomeric poison cheap compared with enantiomeric chiraphos-rhodium. In a demonstration of the chirally poisoned catalyst system, Faller uses it to reduce α-methylenesuccinic (itaconic) acid to α-methylsuccinic acid in 49% enantiomeric excess.

Continued on page 57

'Chiral pool' furnishes amino acids for chemical syntheses



Source: SmithKline Beecham Pharmaceuticals



Celgene's new 700-gal reactor at Warren, N.J., exemplifies growing recognition by chirotechnology companies that they need synthetic chemical as well as biotechnological capabilities.

Asymmetric syntheses

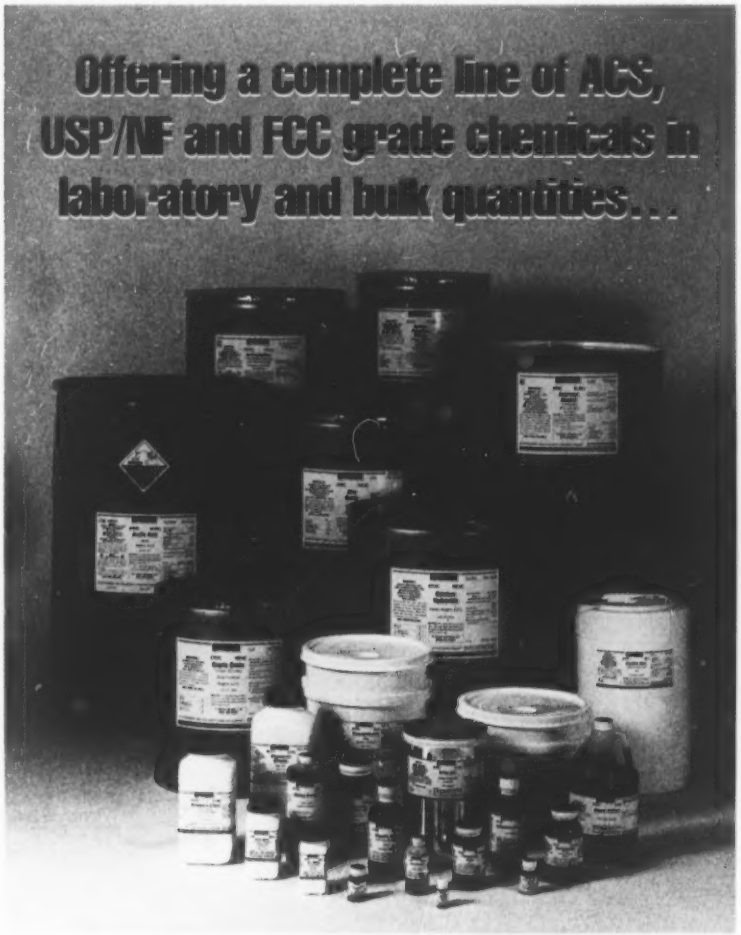
Theoretical and practical work show how much progress has been made in asymmetric reduction of ketones to enantiomeric secondary alcohols. But chemist Hans-Ulrich Blaser of Ciba in Switzerland says similar progress is lacking in the all-important problem of reducing imines ($R_2C{=}N\text{-}R$) to enantiomeric amines. Amines are important in medicinal chemistry.

Blaser explained at Chiral Europe '94 in Nice that imine Schiff bases form readily from amines and carbonyl compounds. But reactions are often incomplete, and trimers and other longer congeners also generally form. Schiff bases are additionally unstable to hydrolysis. And there is the problem of geometric syn-anti isomerism about the C=N bond.

The asymmetric hydrogenation catalysts now available are not very active toward imines and need high temperatures and pressures to succeed. But Blaser says that hydrogenation is still the best bet. This is because hydrogenation leaves no reagents to recover and no boron or aluminum wastes to dispose of. Blaser is optimistic that hydrogenation catalysts will allow imine production to approach that of secondary alcohols. There are increasing numbers of enantiomeric diphosphine ligands becoming available, he says, and experiments on their chelates with iridium, rhodium, and ruthenium may lead to the needed activity.

Another tactic in asymmetric synthesis is use of chiral synthons. These synthons are enantiomeric compounds that serve as starting materials and whose own chirality induces the desired chirality during the reactions that follow. One recent application is that of chemist Lendon N. Pridgen of SmithKline Beecham Pharmaceuticals in King of Prussia, Pa.

As Pridgen explained in Nice, his synthetic chemistry department received an internal request for large amounts of (*R*)-α-*p*-bromophenylethylamine as a resolving agent to separate a racemic carboxylic acid in production of a single-isomer drug. Pridgen's solution was to use the chirality of (*R*)-phenylglycinol, which was also to provide the amino group. Treatment of that with *p*-bromo-



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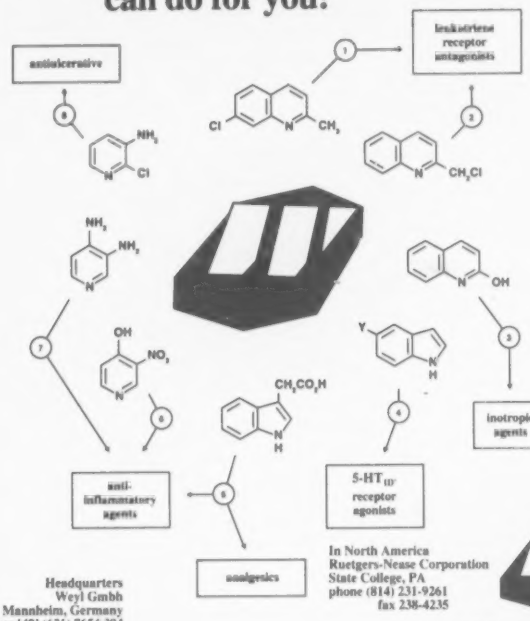

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Exploring a world of mirror images

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"How would you like to live in Looking-glass House, Kitty? I wonder if they'd give you milk in there? Perhaps Looking-glass milk isn't good to drink."

—Lewis Carroll, "Through the Looking-Glass," 1871

benzaldehyde yielded an enantiomeric oxazolidine, which now also contained the needed *p*-bromophenyl group. Reaction with methylmagnesium chloride added a methyl group, and oxidation with lead tetraacetate freed up the phenylethylamine product.

Process research manager David Tapolczay of Glaxo Research & Development, Greenford, England, also described the chiral synthon approach at Chiral Europe '94 in searching for ways to make cyclopentane aminoalcohols. Such aminoalcohols mimic ribose and deoxyribose in antiviral drugs. The particular target was a single enantiomer of a 4-amino-2-hydroxymethylcyclopentanol.

Tapolczay turned to a popular starting material known as Vince's lactam (2-azabicyclo[2.2.1]hept-5-en-3-one). He worked out routes to the desired cyclopentane derivative beginning with racemic or enantiomeric lactam and proceeding by way of single-isomer methyl 4-benzamino-2-cyclopentenecarboxylate. Two other firms active in enantiomers of both Vince's lactam and the carboxylate are Chiroscience, Cambridge, England, and Lonza of Basel, Switzerland, and Fair Lawn, N.J. So Glaxo is also able to buy intermediates from them.

While Pridgen and Tapolczay cite use of chiral synthons to solve individual problems, organic chemistry professor Dieter Enders of the Rhine-

Westphalia Institute of Technology, Aachen, Germany, has created a whole cottage industry out of chiral auxiliaries that he calls SAMP-RAMP. Chiral auxiliaries are enantiomeric compounds that are temporarily attached covalently to a substrate. The auxiliaries induce desired chirality during later reactions on the substrate. Finally, the auxiliaries are cleaved and, chemists hope, recovered. SAMP and RAMP are (*S*)- and (*R*)-1-amino-2-methoxymethylpyrrolidines.

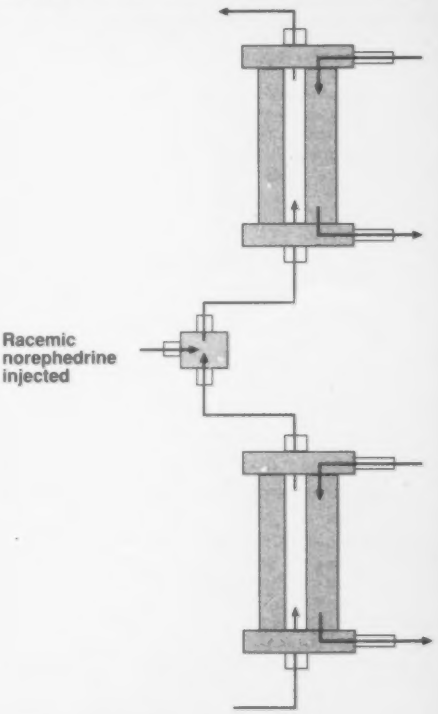
Because these auxiliaries are hydrazines, one reaction they undergo is formation of hydrazones with ketones. The hydrazone function sets up the rest of the molecule for further reactions, and the chirality of the pyrrolidine induces the desired chirality in the reacting substrate at the same time. The hydrazones can be cleaved at the end of the reaction sequence.

One of Enders' examples in Nice was the synthesis of so-called (*S,S*)-A-74,704, a human immunodeficiency virus (HIV) protease inhibitor that is a candidate drug for treating AIDS. The starting material is the acetonide of dihydroxyacetone (2,2-dimethyl-1,3-dioxolan-5-one). Enders uses SAMP to form a hydrazone, then a combination of butyllithium and benzyl chloride to introduce a benzyl group adjacent to each side of the C=N bond forming two new asymmetric carbon atoms in the desired configurations. Later in the sequence, the SAMP hydrazone is converted back to the ketone, which is reduced to a hydroxyl group that occurs in the final drug product.

Both SAMP and RAMP are now commercially available from Oxford Asymmetry, Abingdon, England, which offers chiral auxiliaries developed by many academic chemists worldwide. Oxford Asymmetry was originally founded by organic chemistry professor Stephen G. Davies of nearby Oxford University, with funding from outside investors, in order to commercialize his own compounds.

Indeed, the newest products from Oxford Asymmetry are Davies' own enantiomeric 5-methoxymethyl, 5-ethoxymethyl-, 5-trityloxymethyl-, and 5-*tert*-butyldimethylsilyloxymethyl-3,3-dimethyl-2-pyrrolidones, made from L-glutamic acid. These compounds are

Countercurrent extraction separates drug or intermediate enantiomers



1. Heptane solutions of tartrate esters are separated by water-saturated cellulose membranes.
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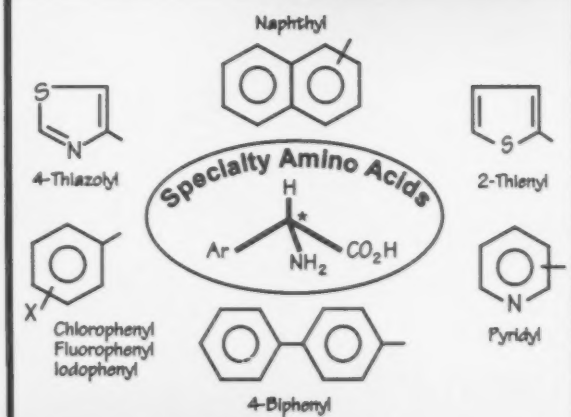

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designed to bond to substrates at the pyrrolidine nitrogen, induce the desired chirality in the substrate during subsequent reaction, and then be easily hydrolyzed.

Biotransformations in syntheses

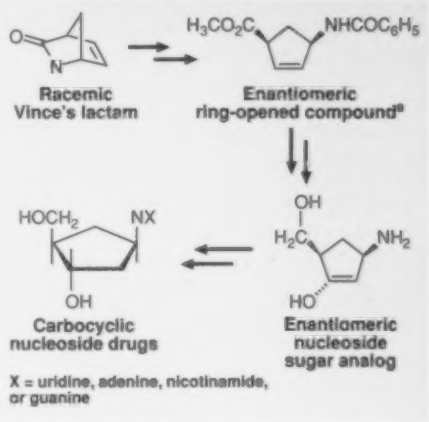
In addition to synthetic organic chemical approaches to asymmetric syntheses and resolutions of racemates, biotransformations have become key technologies, with many firms serving the drug industry. Many startup firms that began with biotransformations have found it necessary to add synthetic chemical capabilities.

Lonza is the newest company to add biotransformations to its existing synthetic organic technologies. The firm has acquired a fermentation plant in Kouřim in the Czech Republic. Biotechnology manager Olwen M. Birch described at the Nice conference how Lonza coordinates its chemical production in Visp, Switzerland, with the new biotechnological capabilities in Kouřim.

One such project is production of cilastatin, a drug originally discovered by Merck to prolong the lifetime of β-lactam antibiotics in the body. Cilastatin is an N-substituted (*S*)-2,2-dimethylcyclopropanecarboxamide. Several chemical routes to the compound are possible, beginning with the synthesis of racemic 2,2-dimethylcyclopropanecarbonitrile from readily available starting materials.

Switching to biotransformations, Lonza uses a nonstereoselective nitrile hydratase to catalyze conversion of the nitrile to racemic amide, and an amidase to hydrolyze the (*R*)-amide preferentially to the (*R*)-carboxylic acid, leaving the desired (*S*)-amide for cilastatin production. Switching back to chemistry, Lonza reacts the (*R*)-acid first with thionyl chloride, then with ammonia, to get back to the racemic amide. This recovered racemic amide is combined with more racemic amide from hydrolysis of nitrile, thus enabling a theoretical 100% conversion of starting material to the (*S*)-amide.

Glaxo synthetic route leads to aminoalcohol nucleoside analogs



a Also available commerically from Lonza.
Source: Glaxo Research & Development

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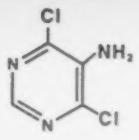
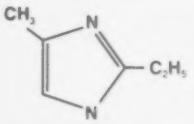
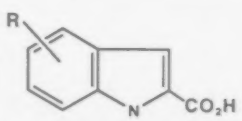
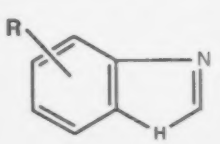

5-Amino-4,6-Dichloropyrimidine

Pyridine N-Oxide


2-Ethyl-4-Methyl-Imidazole


Indole-2-Carboxylic Acids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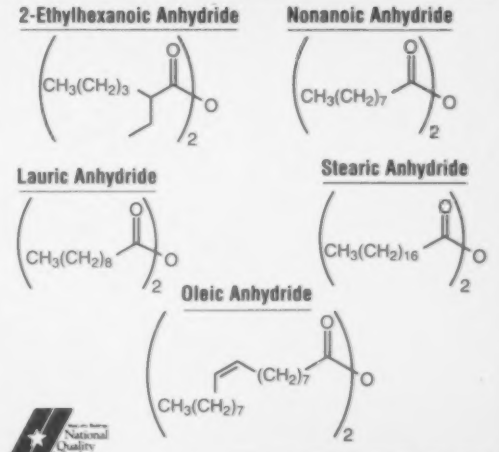

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Kaneka Corp. of Osaka and New York City has entered production of enantiomeric chemicals with a broad effort in biological methods. Industry observers rank Kaneka about neck-and-neck with the Andeno division of DSM Fine Chemicals in magnitude of chiral intermediates production. The company has a 1 million-kg-per-year amino acid plant in Singapore, that produces, among other compounds, D-phenylglycine and D-*p*-hydroxyphenylglycine as side chains for β-lactam antibiotics.

And another biological strength of Kaneka is immobilization of plant and animal tissue cells in polyvinyl formal resin. Drug company customers supply their cell lines, and Kaneka uses immobilized cells to produce bioproducts.

But the firm's plant in Takasago, Japan, also includes a full battery of equipment for synthetic chemistry. Marketing and development manager

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Conferences and expos introduce chiral drugs

Two series of annual symposia and expositions have become established in both the U.S. and Europe to present the latest offerings in enantioselective compounds, auxiliaries, technology, and services to customers. One of these, Chiral Europe '94, met this week in Nice, France. Meanwhile, Chiral USA '95 will be held in Boston, May 15–16, 1995.

Chiral matters often also form parts of conferences and exhibitions on fine chemicals, generally. For example, Chemical Specialities USA '94 will meet in Chicago, Oct. 18–20. One paper will address enantiomeric phase-transfer catalysts, and many exhibitors will feature enantioselective technology. ChemSpec Europe '95 will be held in Essen, Germany, June 20–22, 1995.

And for anyone especially interested in custom production of enantiomeric chemicals, the 10th Annual Informex Trade Show & Technical Symposium will be held in Nashville, Feb. 20–22, 1995.

Both Chiral USA and Chiral Europe symposia are organized by Spring Innovations, Stockport, England. Chiral USA '95 will feature 20 papers, delivered over two days by consultants and industrial and academic chemists, and an exhibit. Anyone in North America interested in Chiral USA '95 should contact Brandon Associates, P.O. Box 1244, Merrimack, N.H. 03054; phone (603) 424-2035. Those interested in Chiral Europe '95 should contact Spring Innovations, 216 Moss Lane, Bramhall, Stockport SK7 1BD, England. Phone number from the U.S. is 011-44 (61) 440-0082; fax 440-9127.

Chemical Specialities USA '94, also organized by Spring Innovations, will feature a symposium of 17 papers over two days and an exposition with more than 100 exhibitors. Brandon Associates is also the North American contact for this event.

Informex is sponsored by the Synthetic Organic Chemical Manufacturers Association (SOCMA) and focuses on custom chemical production. Many exhibitors feature enantioselective technology. Next year's meeting features a technical session, whose program is not yet fixed, and a two-day exposition. For information, contact SOCMA, 1330 Connecticut Ave., N.W., Washington, D.C. 20036; phone (202) 659-0060.

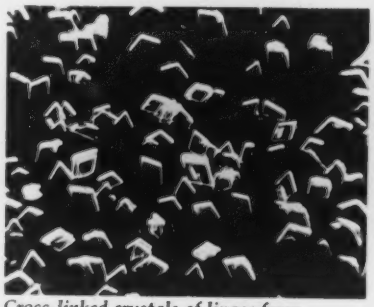
Joseph M. Marasco points with particular pride to the capability to run Birch reductions (dissolving sodium in liquid ammonia) at −100 °C. For this, the Takasago plant uses a Freon circulating to the reactor from a refrigerator compressor. As Marasco puts it, "We're not just 'the D-amino acid company.'" The firm does not bother with resolution of racemates, preferring instead to do asymmetric syntheses and enantioselective biotransformations.

Degussa has long used such a combined chemistry-biotransformation approach to make amino acids at its Rexim subsidiary in Courbevoie, France. Chemist Matthias Kottenhahn of the company's research center in Hanau, Germany, described the Degussa-Rexim approach to both D- and L-amino acids at ChemSpec Europe '94 in Manchester, England.

Such natural, protein-related L-amino acids as L-methionine are used in large volumes as animal feed additives.

Altus Biologics photos

Cross-linked crystals of the protease thermolysin catalyze peptide syntheses.



Cross-linked crystals of lipase from **Candida rugosa** *enable resolutions of and syntheses for a broad range of chiral acids, alcohols, and esters.*

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The Degussa-Rexim process begins chemically with a classical Strecker conversion of aldehydes to racemic hydantoins with hydrogen cyanide, ammonia, and carbon dioxide. For L-methionine, the aldehyde is β-methylthiopropionaldehyde, and for D-alanine, it is acetaldehyde. The methionine hydantoin is hydrolyzed and acetylated to racemic *N*-acetylmethionine.

In a switch to biotransformation, an aminoacylase hydrolyzes only the L-acetylmethionine and leaves the D-isomer. That D-isomer is then racemized and the racemate sent back through the aminoacylase step.

In the route to D-alanine, the appro-

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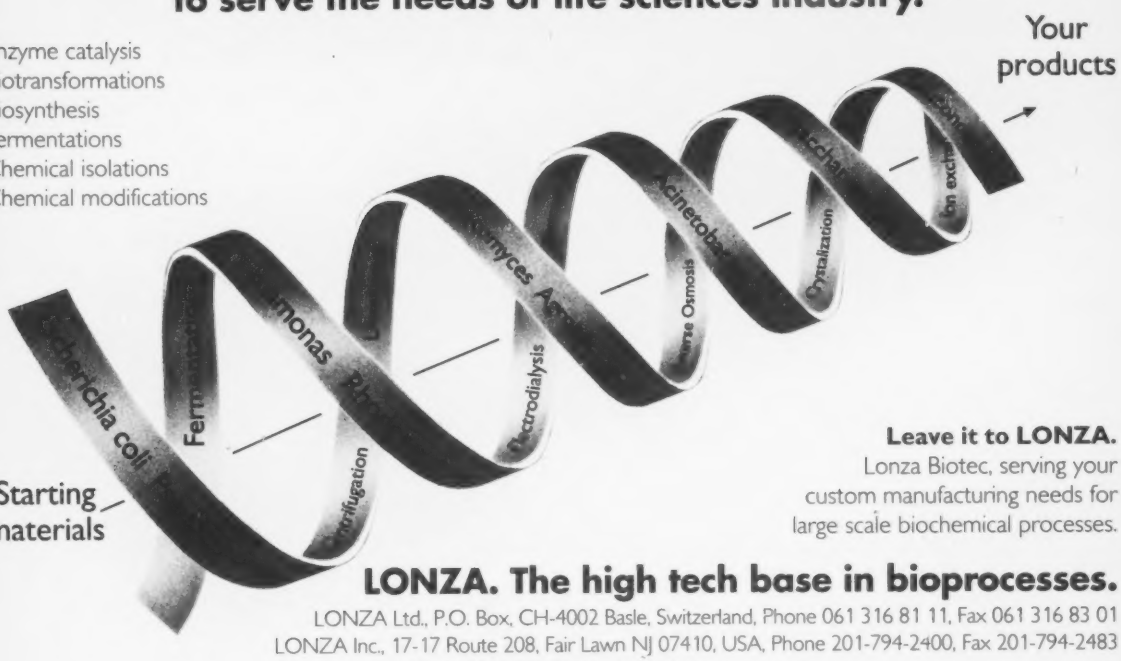

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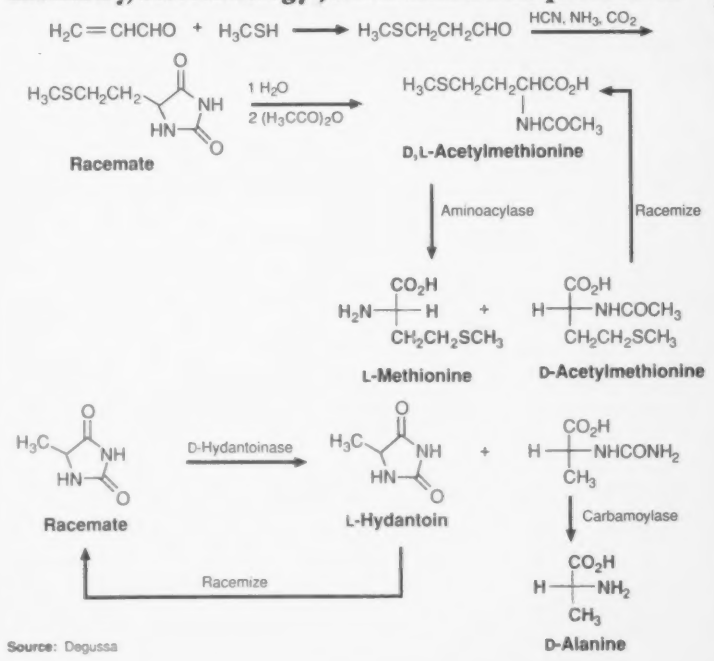
CIRCLE 48 ON READER SERVICE CARD

priate chemically produced racemic hydantoin is acted on by a D-hydantoinase, which hydrolyzes only that isomer, and then a carbamoylase, which frees up the D-alanine. Kottenhahn says that Degussa uses a biomass that has both D-hydantoinase and carbamoylase activity. The L-hydantoin is racemized and sent back through the bioresolution step.

At a large firm like Degussa, which can count on markets for large volumes of amino acids, it is possible to invest significant amounts of money to develop and perfect enzymes and processes. The picture is different for a smaller company like Celgene Corp. of Warren, N.J. Celgene must respond quickly to drug company orders for enantiomeric intermediates. Yet the probability is high that the particular drug will fizzle owing to sudden discovery of unacceptable side effects. Then Celgene could be stuck for all of the development costs to that point.

George W. Matcham, Celgene vice president and general manager for chiral products, explains that the company has responded by developing a very few key enzymes to high degrees of versatility. The result is that when a

Chemistry, biotechnology join in amino acid production



Source: Degussa

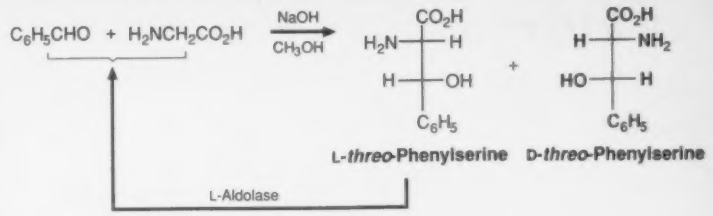
drug firm customer comes with an order for a highly specific single-isomer intermediate, Celgene will already have the enzyme needed to make it.

The company has concentrated on aminotransferases, aldolases, and a trio of nitrile-hydrolyzing enzymes. Aminotransferases catalyze reductive transfer of amino groups from amines to carbonyl compounds. An example is reaction of racemic α-phenylethylamine with propionaldehyde catalyzed by an (*S*)-aminotransferase to produce acetophenone and *n*-propylamine, leaving (*R*)-α-phenylethylamine unaffected as the desired product.

The original aminotransferases come from species of Bacillus and Pseudomonas bacteria, Matcham explains. Celgene inserts multiple copies of the genes for the enzymes into *Escherichia coli*, which are forced to overexpress them. This results in biomass containing large amounts of aminotransferase protein. The company also mutates genes by amino acid substitution or stress to improve their acceptance of certain substrates. The upshot has been the ability to make single-isomer amine intermediates at a cost of less than $1.00 per kg for the amino transfer step.

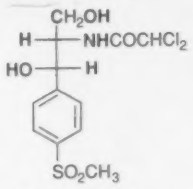
In one project that Celgene has permission to discuss, the company responded to an order for 2.9 kg of (*R*)-4-amino-1-(3-pyridyl)pentane from Hoffmann-La Roche of Nutley, N.J., which Roche wanted for use in making an experimental blood platelet activating

Chemistry and biotransformation make amino acids . . .



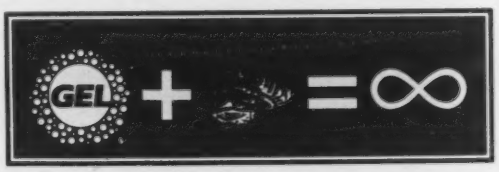
L-*threo*-Phenylserine D-*threo*-Phenylserine

. . . which can be useful for drug production



Thiamphenicol

Source: Celgene



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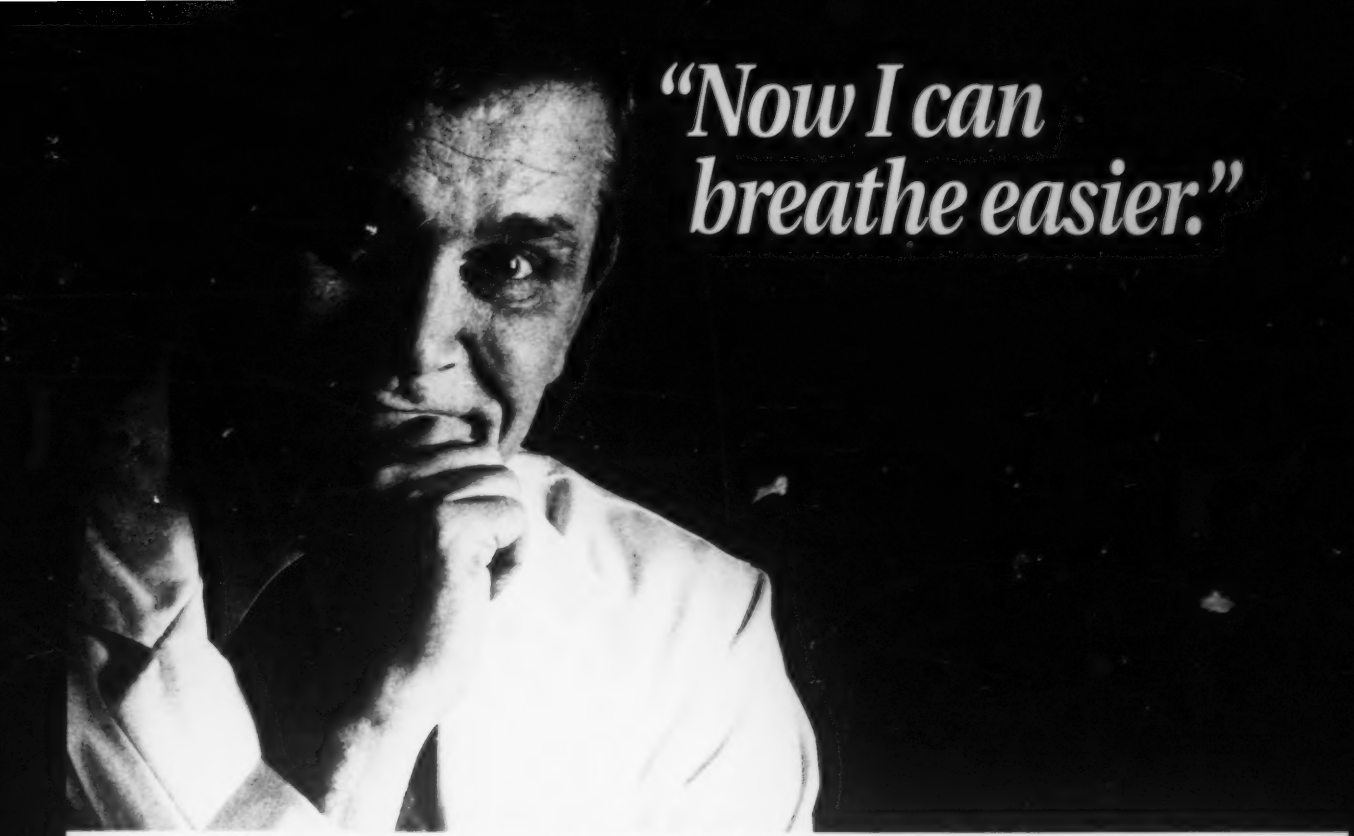


CIRCLE 73 ON READER SERVICE CARD

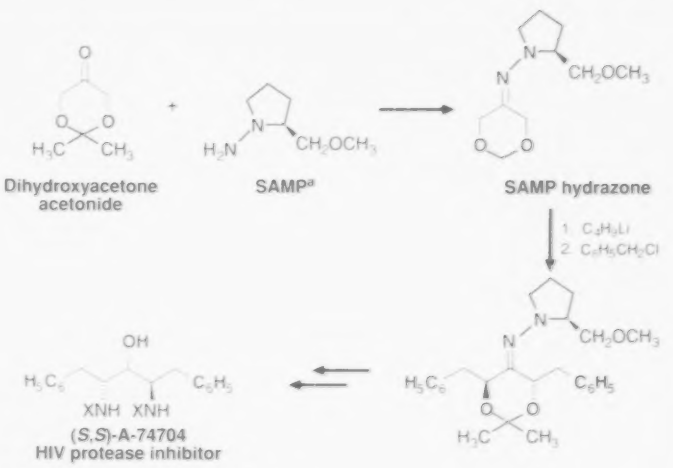
factor as a cardiovascular drug. Roche supplied the racemic amine. An off-the-shelf enzyme at Celgene converted the (*S*)-amine to a ketone, leaving the (*R*)-amine in more than 99% enantiomeric excess. Roche took back the ketone and subjected that to reductive amination (reaction with ammonia and hydrogen over Raney nickel catalyst) back to racemic amine.

An example of the use of aldolases is production of enantiomeric phenylserines. The D-*threo*-phenylserine isomer in particular is an intermediate in manufacture of such "phenicol" antibiotics as thiamphenicol. Just as Celgene can combine chemical conversions of ketones to racemic amines with enzymatic transaminations of racemic amines to enantiomeric amines and ketones, so the company can make racemic serine derivatives by chemical aldol condensations and degrade the unwanted isomer with an aldolase.

For phenylserines, Celgene condenses benzaldehyde with glycine. The condensation is reversible, and the threo-diastereoisomer drops out of solution preferentially. An L-aldolase degrades L-*threo*-phenylserine back to benzaldehyde and glycine, leaving the desired D-threo-enantiomer. Benzaldehyde and glycine can be recycled back to the racemic *threo*-phenylserine.

Though Celgene started out as an "enzyme company," the management has since realized that it needs synthetic chemical capacity as well. At the Warren site, Celgene has installed a

Method mobilizes aldehydes and ketones asymmetrically



a SAMP = (*S*)-1-amino-2-methoxymethylpyrrolidine. The R-isomer (RAMP) can be substituted.
Source: Rhine Westphalia Institute of Technology

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CIRCLE **73** ON READER SERVICE CARD

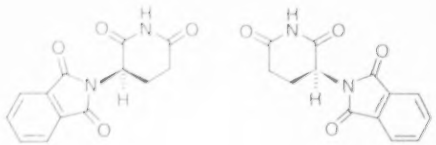
The recrudescence of thalidomide

In discussions of chiral drugs, thalidomide is sometimes cited as a prime example of a drug that differs strikingly in the properties of its two enantiomers. It is alleged that only one enantiomer causes birth defects, whereas the other does not. Thalidomide was developed by Chemie Grünenthal of Aachen, Germany, in the mid-1950s as a sedative to prevent nausea during pregnancy.

In 1961, the compound was found to produce fetal limb abnormalities called phocomelia when taken in the first three months of pregnancy. Most countries promptly yanked thalidomide from the market. The U.S. narrowly averted approving it.

But in 1979, investigators at the University of Bonn, Germany, resolved thalidomide and reported that only the (*S*)-(−)-enantiomer is teratogenic in one strain of mice and Natal rats, and the (*R*)-(+)-form is not. To many people, the Bonn report has indicated that an innocuous enantiomer of thalidomide might yet be salvaged as a useful agent.

The matter involves more than just some effort to market one more sedative. Thalidomide has been found to inhibit replication of the AIDS virus, to clear oral canker sores in AIDS and other patients, and to ease erythema nodosum leprosum reactions (inflammatory skin flareups) in patients with leprosy, also called Hansen's disease. Indeed, doctors treating leprosy patients in the U.S. can get thalidomide from the National Hansen's Disease Center in Carville, La.



R *S*

Also in the U.S., Celgene Corp. of Warren, N.J., has begun Phase II testing (clinical tests in a few hundred ill persons) of its Synovir brand of racemic thalidomide to treat weight loss in AIDS patients. Such weight loss seems related to abnormally high levels of the immune system messenger substance tumor necrosis factor-alpha (TNF-α) in AIDS. The clinical tests may provide results to indicate that thalidomide can reduce high levels of TNF-α.

But as to differences between enantiomers, studies as early as 1967 at St. Mary's Hospital Medical School in London showed that both enantiomers of thalidomide are teratogenic in rabbits. And investigators at the University of Münster, Germany, found in 1984 that each enantiomer racemizes at physiological pH in test tubes or after injection into rabbits. These findings suggest that both enantiomers of thalidomide may be teratogenic in humans and that, in any case, either enantiomer of thalidomide would racemize once in the human body.

700-gal glass-lined reactor to handle swaps back and forth between chemistry and biotransformations. And the firm is looking to buy a large production plant.

One company that has been wedded to classical resolution chemistry is Zeeland Chemicals, Zeeland, Mich., a part of Cambrex Corp. Zeeland uses enantiomers of mandelic acid to resolve racemic amines by fractional crystallization of diastereoisomeric salts. And it uses enantiomers of α-phenylethylamine to resolve carboxylic acids. Indeed, business development manager James K. Datson says the company's newest products are single isomers of α-*p*-methoxyphenylethylamine and *N*-benzyl-α-phenylethylamine as resolving agents and drug intermediates.

But Datson adds that Zeeland is moving into enzymatic methods of resolution. Nothing has yet been decided, but Zeeland's managers realize that the company needs to add biotransformations to its capabilities.

Netherlands-based DSM Andeno is deepening its already broad involvement in biotransformations. DSM Andeno is the fine chemicals division of DSM Fine Chemicals. Andeno founded Chemferm, a joint-venture company, with Royal Gist-Brocades of the Netherlands at the beginning of 1994. Gist-Brocades is a major producer of penicillins, baker's yeast, and detergent enzymes. Chemferm is headquartered in the Netherlands and has a plant in Spain.

Chemferm will concentrate on production and marketing of bulk semisynthetic cephalosporin antibiotics. It is possible that Chemferm will be able to use aqueous enzymes to couple such side chains as D-phenylglycine onto the fundamental 7-aminocephalosporanic acid nucleus without needing to use the acid chloride in methylene chloride solvent. And in a further advance, Chemferm may discover an enzymatic process to use even cheaper racemic phenylglycine and couple only the D-enantiomer to the antibiotic.

A new direction in enzyme technology is the cross-linked enzyme crystals of Altus Biologics, Cambridge, Mass. Altus is a subsidiary of Vertex Pharmaceutics, a startup drug company also located in Cambridge.

Research director Alexey Margolin says Altus has added a cross-linked crystalline lipase from the yeast *Candida rugosa* to its peptidase product thermolysin. The lipase catalyzes a broad range of esterifications as well as hydrolyses. The thermolysin stitches peptides together and also breaks them down.

Altus first crystallizes the enzymes, then treats the crystals with glutaraldehyde. Bifunctional glutaraldehyde cross-links enzyme peptide chains by Schiff base reaction with pendant amino groups of lysine residues. Because the crystals are of single enzymes, Altus products avoid contamination with other enzymes that can occur in crude enzyme preparations. And cross-linked crystals function in such unusual solvents as 90% aqueous ethanol, 50% aqueous methanol, and pure ethyl acetate or dimethylformamide, as well as at temperatures as high as 55 °C.

Margolin gives selective hydrolysis of racemic methyl ester of ibuprofen to (*S*)-(+)-ibuprofen in 95% enantiomeric excess as an example of cross-linked lipase capability. And the protease can be used to assemble the three L-amino acids of the artificial sweetener aspartame.

The chirotechnology industry in the second half of the 1990s will see a growing number of participants and a growing number of capabilities. Early in the development of the industry, companies such as Bend Research of Bend, Ore.; Celgene, Chiroscience, Genzyme Corp. of Cambridge, Mass.; Peboc of Gwynedd, Wales; and Sepracor emerged as small firms operating in particular technology niches.

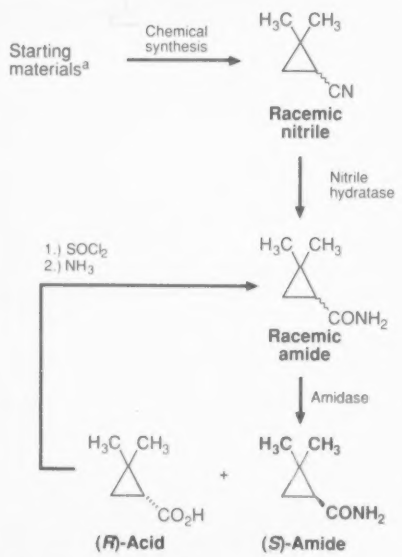
But as the chirotechnology industry has evolved, these companies have come to realize that their drug industry customers want products, not licenses to use proprietary technologies. As a result, these companies have begun to acquire commercial-scale production plants.

Other trends are apparent, as well. Companies that specialize in biotransformations are adding enantioselective synthetic organic chemistry to their portfolios. Large and small firms whose roots were in synthetic chemistry are developing or acquiring biological methods. DSM Andeno, for example, has sought a joint venture with enzyme specialist Gist Brocades. Lonza has bought a fermentation plant in the Czech Republic.

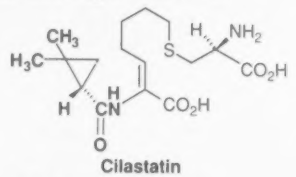
Companies that do not buy plants, develop new technologies, or enter joint ventures can expand their capabilities by means of informal alliances with one another. Examples are the cases of Chiral Technologies with UOP and Sepracor with Separex Chimie Fine.

The combination of these trends suggest that, in coming years, the chirotechnology industry is likely to evolve toward a few dozen uniformly capable companies that differ little from one another except in size. □

Synthesis and biotransformation combine to make intermediate . . .



. . . that is useful to produce an antibiotic potentiator



a Several routes are known. **Source:** Lonza

Five multiple firings detailed in report

The latest report on multiple terminations by the Subcommittee on Professional Standards & Ethics of the Council Committee on Economic & Professional Affairs (CEPA) gives details of five such terminations that occurred between August 1992 and June 1993. These terminations involved 95 job losses by chemical professionals.

The report, the 38th in a series dating back to 1974, indicates that an additional three multiple terminations have been verified and 16 as yet unverified reports are currently under investigation.

A multiple termination, as defined by CEPA, is a situation in which the employment of three or more chemical professionals is terminated by a single employer within a six-month period for reasons other than continuing evidence of previously documented inadequate performance, completion of a contract, or cause.

The reports have always been concerned only with job losses that are clearly involuntary. They do not provide a mechanism for investigating the "voluntary" separations and early retirement programs that have pervaded the chemical and related industries in recent times. Thus, the reports may not accurately reflect the employment picture for some chemical professionals.

According to the report, the committee's goal is "to provide an unbiased view of these terminations by gathering data from both the employer and the terminees ... and to accurately and fairly describe contemporary industry practices to both chemists and their employers, so that expectations are grounded in recent experience, not myth or rumor."

But there have been numerous problems gathering information from terminees and from employers. In the current report, no employers agreed to provide details about their staff reductions. According to the report, "Typically, a company declines to participate, stating that they do not discuss personnel actions with those outside the company." For these and other reasons, these reports are slated to be discontinued after the next one is approved. CEPA will, however, continue to monitor and publish employment information via other sources.

The five multiple terminations detailed in the latest report were at A. D. Little, Cambridge, Mass.; Dow Chemical, Midland, Mich.; Koch Protective Treatment, Dayton, Ohio; Miles Inc., Tarrytown, N.Y.; and UOP, Tarrytown, N.Y. The largest was at Dow with 30 confirmed involuntary separations; the smallest was at UOP with four.

The three verified multiple terminations for which CEPA investigations are not yet complete were at DuPont, Twin City Testing, and Rohm and Haas.

As usual, the latest report compares the performance of employers with standards spelled out in ACS's Professional Employment Guidelines (PEG). These standards are concerned with advance notice, severance pay, assistance in finding new employment, length of employee service, and employee protection after termination.

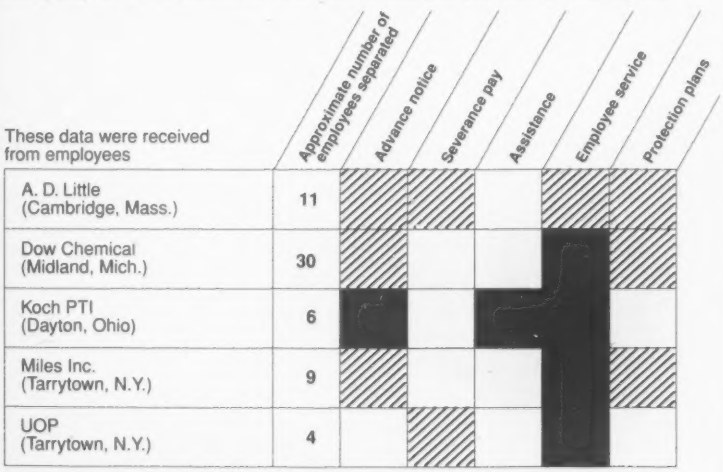
Overall compliance with the PEG standards has remained fairly constant over the years. For the first 19 reports, through mid-1984, compliance was 42%; since then, it has been 44%. For this report, it was 42%.

The most discouraging news comes in the drop in compliance in meeting employee service standards. PEG standards call for no terminations of employees who have 10 years or more of service.

ACS Professional Employment Guidelines

- Advance notice. **Minimum of four weeks.**
- Severance pay. **Minimum is two weeks per year of service. Additional notice may be given, by mutual agreement, in lieu of severance pay.**
- Assistance. **Efforts should be made to place terminee in another position within the organization, or terminee should be given assistance to find employment elsewhere.**
- Employee service. **Those with minimum of 10 years' service should not be terminated except for continued evidence of previously documented inadequate performance or cause.**
- Employee protection plans. **Should be extended for a minimum of one month, plus two weeks for each year of employee service, following termination, at same rate of contribution as before. Employee would have additional 31-day grace period.**

Employer compliance with ACS employment guidelines



☐ Employer met or exceeded guideline standard.

▨ Two or more individuals below guideline standard, but average experience better than "substantially below" criterion.

■ Employer was substantially below guideline standard, which is defined as follows:

- Advance notice—less than four weeks.
- Severance pay—less than two weeks per year of service.
- Assistance—no assistance rendered.
- Employee service—more than 30% of terminees had 10 or more years of service.
- Protection plans—no continuation of protection plans.

For the first 19 reports, compliance was 26%; since then, it has dropped to 14%. None of the employers in the current report complied with standards in this category. About 48% of all terminees in the current report appear to have had more than 10 years of service; among these, the average length of service was approximately 19 years.

Also slipping was compliance with PEG standards that call for four weeks' advance notice of termination. In the latest report, four of five employers—A. D. Little, Dow Chemical, Koch, and Miles—failed to meet this standard. UOP exceeded this guideline standard; all terminees reported between nine and 10 weeks' notice. Koch fell substantially below guidelines. Throughout the years, compliance with this standard has remained steady at about 40%.

The bad news may have been partially offset by some evidence of improvement in meeting the severance pay standard of two weeks' pay for each year of service. For the first 19 reports, only 16% of employers complied. For the second 19, compliance was 49%. This report indicated 60% compliance.

Compliance with the employee assistance standard has improved throughout the years, coming in at 80% for this report. The first 19 reports indicated 65% compliance; since then, compliance has risen to 85%. In the current report, only Koch failed to offer terminees résumé preparation and other services.

The PEG standard on protection plans calls for continuation of health insurance at employer expense for at least one month beyond separation. Compliance, 48% for the past 20 years, has declined during the past 10 years to 34%. The figure for the current report is 40%. Under the Consolidated Omnibus Budget Reconciliation Act of 1985, however, a terminee is entitled to continuation of benefits for up to 18 months. Inconsistent reporting of employers' actions—because of the widely different terms—may be the primary reason that employers appear to be falling short on meeting this PEG guideline.

Chemical professionals who have been fired or have taken early retirement are requested to contact the American Chemical Society, Office of Professional Services, 1155—16th St., N.W., Washington, D.C. 20036. Copies of all related C&EN stories are available, on request, from the same office.

Linda Ross

Undergraduate program popular at ACS meeting

The ACS national meeting in Washington, D.C., featured the first comprehensive program for undergraduates at a fall meeting. Activities designed specifically for undergraduate chemistry students drew nearly 400 participants.

Programming was designed to help students plan for the future by giving them the opportunity to learn about graduate schools, offering employment assistance and career information, and providing opportunities for networking with faculty and students from other schools.

Over the past several years, the Society Committee on Education (SOCED)—through its task force on undergraduate programming and the student affiliates program office—has been working to increase undergraduate participation in national meetings. Recognition of the importance of students to the future of the society and of the profession is prompting various ACS operating groups to jump on the undergraduate bandwagon.

In Washington, activities were sponsored by SOCED; Corporation Associates; the Younger Chemists Committee; the divisions of Chemical Education and of Small Chemical Businesses, the ACS staff offices of Local Section Activities, Public Outreach, and Career Services; and the National Chemistry Week Task Force, among others.

One of the most popular events on the program was a graduate school fair and reception. The event featured displays from 60 graduate departments and drew many interested students. Terri Nally, manager of the ACS Office of College Chemistry, reports that many graduate school representatives were delighted at the turnout—particularly at the proportionately large number of minority students at the fair. "If even a fraction of the students that we've seen talking to graduate school faculty end up applying to those programs, the effect on admissions of minority students to graduate chemistry programs at many schools could be profound," Nally says.

In addition to representatives from graduate programs and potential students getting to know each other, tips on the ins and outs of graduate school admissions were given by George Pfeffer, associate professor of chemistry at the University of Nebraska, Omaha. "Any chemistry faculty member has gone through the graduate school application process themselves," says Pfeffer, "so there is a lot of anecdotal information out there in addition to a lot of reference information—much of it produced by ACS." He reports that students were quite pleased to have so much of the information available in one place.

Slayton A. Evans Jr., professor at the department of chemistry at the University of North Carolina, Chapel Hill, helped students prepare for the not-so-distant future of next semester. He presented the meeting's Eminent Scientist Lecture using an interactive style to help students understand some aspects of stereochemistry.

Evans was encouraged by the interaction among students and faculty at the meeting. Our "clear objective [as teachers] should be to ensure that all students learn something new, either directly from the instructor's presentation or by listening to the dialogue between instructor and other students."

He believes that "encouraging and challenging students to share ideas and express their understanding of concepts through in-class dialogue promotes the learning process in a more profound way than simply by lecturing or presenting information." Before and after the lecture, he spent an hour or so talking with stu-

C&EN staff photo

Pfeffer (at left) spoke at the graduate school fair.